Distribution

Introduction

Absorption got the drug into the blood. Now **distribution** will get it from the blood and into the tissues where we want it (the target organ, the intended effect). Distribution also gets the drug to the tissues we don't want to get it to (the non-target organs, the side effects). Since the drug is circulating through the bloodstream, it's going to be sent everywhere. That's not what we mean by "distribution"—we don't mean "distributed throughout the body in circulation." The way we are using distribution in this lesson is a characteristic of a drug: **how well the drug leaves the plasma**.

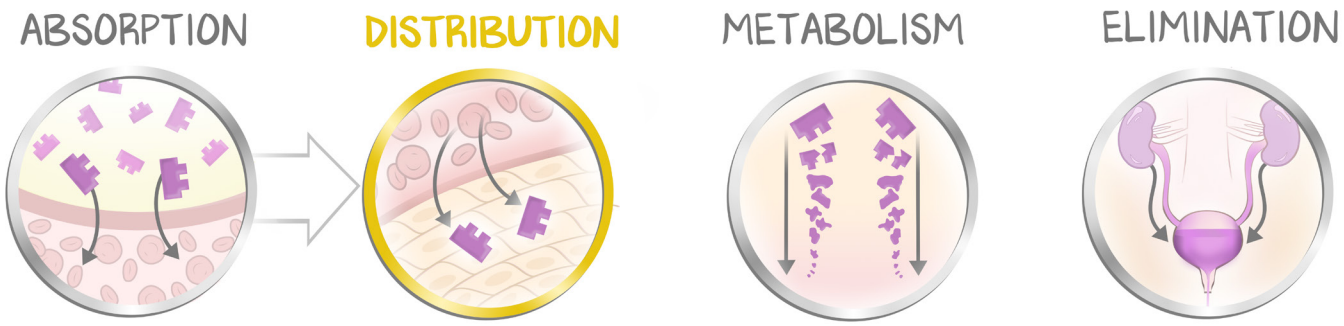

Figure 3.1: Pharmacodynamic Map, Distribution
Distribution is the process through which the drug leaves the blood and moves into tissues.

We **don't** want the drug in plasma. We **don't** want the drug in non-target tissues. We **do** want it in the target tissue. But distribution is only how well the drug leaves the plasma—it does not specify or give any insight as to where the drug is going, only that it is leaving the plasma. Period.

Of course, all the while, the drug is being metabolized and eliminated. Although we're looking at distribution as though it's a snapshot, absorption, distribution, metabolism, and elimination are all occurring at the same time.

The drug has already gotten into the bloodstream, and now must pass from the bloodstream into tissues. Distribution is still affected by the diffusion equation—diffusion out of the plasma compartment and into another organ compartment. But now we'll engage in greater detail the correlate of size—how **protein-binding** influences getting the drug out of the tissue. The protein that drugs bind to is **albumin**. Albumin is in the blood, and not anywhere else. Therefore albumin, protein-binding, and the free fraction impact distribution. If bound to albumin, the drug cannot leave the plasma. If free from plasma, it can leave plasma.

We then move into discussing another element of size by looking at **specific endothelial barriers** and their consequences. The drug must get out of the plasma. To do that it either must pass THROUGH the endothelial cells' plasma membrane (lipid-solubility) or be allowed to pass between endothelial cells. Some barriers are tight, others loose. The tighter the barrier, the less gets through, and therefore only drugs that can pass through the membrane will leave plasma.

Finally, we finish up with a mathematical representation of a **drug's "*distribution-ability*"** called the **volume of distribution** (Vd). Distributionability is a word I made up to describe what Vd means. Vd is not a tangible thing, merely a mathematical equation you will be forced to endure on test questions.

"Size" Means "Protein Bound"

The human body has proteins in the plasma. The one we're concerned with is **albumin**. Albumin readily binds other proteins. "Other proteins" includes our drug as well as other endogenous (our own) proteins or exogenous (others') drugs at the same time. Relative to the amount of drug we give, there's **infinitely more albumin**. In a vacuum, where there were only albumin and the drug (and nothing else), albumin would bind all the drug, and none of it could leave the plasma.

Albumin doesn't get filtered. It doesn't end up in the urine. It shouldn't end up outside the capillaries (any time it does, represents a pathologic state, such as an exudative effusion). That's because **albumin is so large it doesn't filter**. So it stands to reason that if the drug is bound to albumin, the drug doesn't filter, either. "Filter" is the word we use in the kidneys; it means the same thing here as "distribute," which means "get out of the plasma."

Bound protein can't do anything and **stays in the plasma**.

Free drug, not bound to albumin, can **leave plasma** and **exert its effect** by getting into tissues. The intended effect is achieved by distribution into the target organ. Side effects result from distribution into other organs.

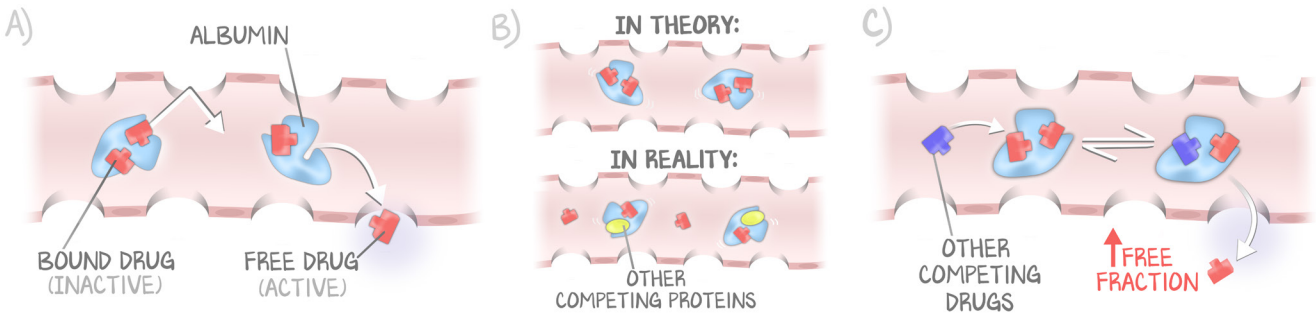

Figure 3.2: Free Fraction and Albumin
(a) Albumin is too large to pass through even the most fenestrated capillaries, so any drug bound to albumin is trapped in the bloodstream. Only free drug NOT bound to albumin can distribute into tissues. (b) In a vacuum, albumin could bind all the drug if only albumin and drug were present, versus reality where many drugs compete for albumin binding, resulting in the drug we give maintaining a free fraction because of displacement by other proteins. (c) This allows for the addition of another albumin-bound drug to displace our already-present drug, leading to toxic side effects.

We're not a vacuum. In real life there are **too many other proteins for the amount of albumin available**. Which means that at any given time, some of the drug will be bound to albumin, and some will be free in the plasma. This is true of our own proteins. It's the relationship of the free protein to bound protein that determines the activity of the drug. The **free fraction** of a drug, at any one time, is **relatively constant**. We could drastically alter the composition of the plasma artificially, but in a real human the amount of albumin there is, plasma pH, and any other factors that determine how well a protein will bind to albumin are more or less fixed. This relatively constant free fraction is made possible by **competition from other proteins**. This is good in the sense that it's physiologic. It's bad in the sense that we could inject another drug which would displace our original drug from albumin, thereby increasing the free fraction, increasing the active drug distributing into tissues, even without altering the dose the person was taking. This is one mechanism for drug-drug interaction.

Barriers to Distribution

Once a drug gets free of albumin, it tries to get out of the plasma and into tissues. Even the free fraction of the drug, that not bound to albumin, cannot just leave the plasma. Blood vessels are lined by a layer of cells called the endothelium. At the level of the capillary, the endothelium is one-cell thick. For a drug to get out of the capillary it either must pass THROUGH the endothelial cell, necessitating that it be lipophilic, or the space between the endothelial cells must be large enough to let the drug pass between them.

The **liver** features an example of **sinusoidal capillaries**. Here, the gap between the endothelial cells is so large that almost everything (albumin is still too large) distributes into the liver. The liver, as we will discover in #4: *Metabolism/Biotransformation*, is the processing organ for toxins. Most drugs are metabolized by the liver. So it makes sense that the liver would permit drugs, toxins, and the like out of the bloodstream and into hepatocytes for processing.

On the opposite side of the spectrum are two endothelial barriers that work very similarly to one another, and both block the passage of drugs into the compartment they protect. They do this by maintaining a **tight endothelial barrier**, such that only those lipophilic drugs that pass through the endothelial cell are permitted; all others are denied passage between the endothelial cells. This means that even if a drug gets free of albumin, **if it's polar**, or **large**, or **charged**, it won't be able to get past this barrier. Only **lipophilic compounds** can get through these barriers.

These are the **blood-brain barrier** and the **blood-placenta barrier**.

We don't want medications getting into our brains or our developing babies if they don't belong there. Drugs that distribute into the brain can cause side effects, and drugs that get into a developing fetus can cause growth defects. And most medications aren't lipophilic at physiologic pH of 7.4, which is good—we administer medications to treat many diseases and they don't get into our brains or into the fetus. But this can also be bad—if we DO want to get a medication into the brain that isn't lipophilic (like **Ara-C**, for CNS chemotherapy in ALL), we must inject it into the CSF, not the veins. Following the same principle, if we DO want to get a medication to the brain (**psychiatric medications** or **seizure medications**), then these medications need to be hydrophobic. That in itself isn't a problem until mom gets pregnant. If the medications for mom's brain are lipophilic enough that they will get into mom's brain, they are lipophilic enough to get into the fetus.

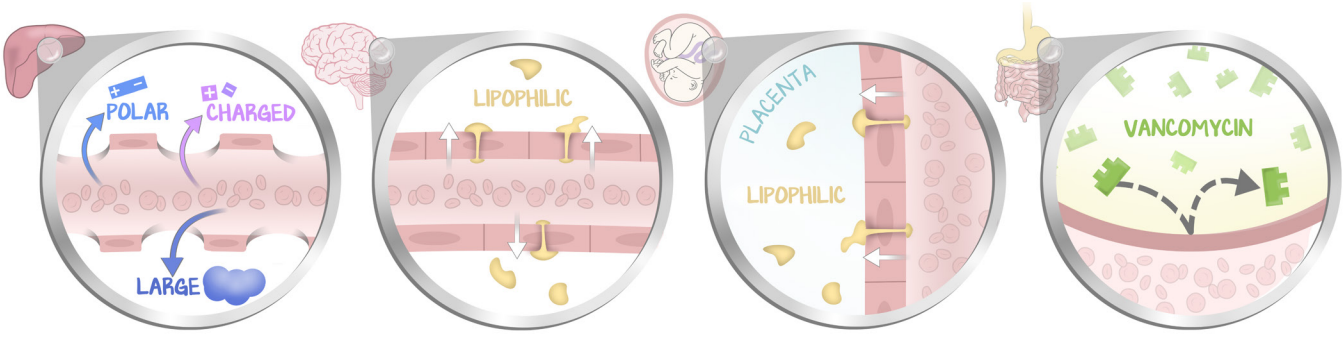

Figure 3.3: Endothelial Barriers
Hepatic capillaries are sinusoidal, letting drugs, proteins, and toxins into hepatocyte circulation for detoxification. The blood-brain barrier has a tight endothelium so that no drugs can flow between cells, necessitating that drugs that cross the blood-brain barrier diffuse through the endothelial cells, and therefore necessitating that these drugs be lipophilic. The placental barrier works the same way, such that those medications that can get into mom's brain can get into the growing fetus, potentially causing birth defects The blood-gut barrier rarely acts as a strong barrier, except for vancomycin, which when ingested orally can fight only intraluminal infections, whereas intravenous vancomycin can treat systemic infections.

The consequences are twofold. First, when mom gets pregnant, we want to use **hydrophilic medications** whenever possible to avoid CNS side effects, but mostly to avoid baby's seeing a teratogen. Second, when mom gets pregnant and **needs CNS medications**, we're stuck riding the line between teratogenicity and mom's disease flaring. In the middle is a compromise—since any medication getting to baby is an unwanted side effect, we can reduce the amount of medications getting to baby by choosing those that have a higher affinity for albumin. Being more protein bound, the free fraction is less, and the less sneaks into baby.

Personally, I think this is bogus Step 1 theory. We used to use PTU in pregnancy for hyperthyroid because it was protein bound. But now we know that PTU and methimazole are equally safe. And logically, if less gets into baby, less gets into mom's brain. But…this concept is everywhere in Step 1 review, so I'm putting it down.

Finally, there is the **blood-gut barrier**. Some drugs just can't get absorbed through the gut, and must be given through a parenteral route. This is NOT because of first-pass metabolism, but because the medication will not be absorbed by the human intestines. Most medications are absorbed by the gut. The one notable exception is **vancomycin**. To treat a *Staph. aureus* infection of the skin, we administer vancomycin intravenously. To treat an intraluminal infection of the colon by *Clostridium difficile,* we administer vancomycin orally. Oral vancomycin doesn't get into the blood, and intravenous vancomycin doesn't get into the lumen of the colon. Although the blood-gut barrier does play a role in a few diseases, you should see it only as an asterisk, an exception.

Volume of Distribution (Vd)

This thing, this concept, is a **mathematical abstraction** that is a **quantification** of how well a drug distributes. It's a mathematical representation that takes everything we've discussed so far into mind—polarity, ionization, pH vs. p*K*, size, albumin-binding, etc.—and answers the question: "*how well does this drug distribute out of the plasma?*" It's not "how well does it distribute into the target tissue"; it's not "how much of this drug will cause a problem vs. intended effect." It's only **how well does this drug get out of plasma**.

Mathematically, the Vd gives us the relationship between the dose given and the concentration of the drug in the blood. To increase the concentration of a drug, increase the dose. Increase the dose, and the concentration in the blood goes up. Concentration is quantity per volume. The volume described is not the volume of the person. It's the **volume of distribution** for the drug. Because the volume of distribution can be in the thousands of liters—many times more than is in a single human being—there is no concrete clinical use to the Vd. But it is used as a variable to solve test problems all the time. Yes—learn the Vd so you can solve for variables on a test question.

We can change the environment, which can change the volume of distribution of this drug in this person. By making the drug more easily leave the plasma, we increase the volume of distribution. Because we make it easier for the drug to leave the plasma, we decrease the concentration of the drug in the plasma, thereby making the Vd higher. So what can we change in the environment?

If we **increase the free fraction** of a drug (through any mechanism, such as adding another competitor for albumin), that means that **more drug is able to get out of plasma**. Key to this concept is that what we measure, the concentration of the drug in the plasma, is the drug stuck in the plasma. If there is an increase in the free fraction, then more of that drug can leave the plasma, which means there will be less drug in the plasma. Less drug in the plasma means that the measured concentration in plasma is lower. If the concentration is lower, then the spot it holds in the volume of distribution equation (the denominator) is lower). A smaller denominator increases the value of the fraction, and so the result is an increase the volume of distribution. **A large volume of distribution means that the drug will more easily distribute.**

Figure 3.4: Volume of Distribution
As the dose of a drug increases, the concentration in the blood will increase. The more distributable a drug becomes (nonpolar, un-ionized, freed from albumin), the more easily it will leave the plasma, and the larger the volume of distribution value will be. Large Vd means "gets out of plasma well."

If instead we **ionize the drug** (through, say, a change in pH), that will cause the drug to become lipophobic, or more hydrophilic. This makes it **harder for the drug to leave plasma**. That means the concentration of that drug in the plasma will increase. Increasing the denominator means that the Vd will go down, get smaller. A small volume of distribution means the drug will less easily distribute. Distribute means "get out of plasma."

This may seem remedial, spending so much time on an equation with two variables. After you do the challenge questions and feel good about yourself, try your hand at lesson #5: *Elimination*, where Vd is just one of many variables the test can use to mess with you.

Redistribution—270+

Some drugs go right where you want them. Phenobarbital, on the first dose, goes right to the brain. It distributes quickly into the target tissue. It also goes to other body compartments such as adipose, but goes there slowly. These other tissues act as reservoirs. The drug distributes into these reservoirs slowly, and comes out just as slowly. This isn't a big deal if there isn't saturation. The initial dose is received, metabolized, and eliminated. The reservoirs continue to leak some of the drug back out, but at such a slow rate that the drug is metabolized and eliminated without reaching minimum effective concentration.

BUT…if you give more doses, the concentration in the blood, in the brain, and in those reservoirs goes up. When the reservoirs are saturated, there is nowhere else for this extra drug to go, so the drug accumulates in the blood. In addition, while there is already extra drug in the blood, as the drug is metabolized and eliminated, there will be redistribution from the adipose (the drug comes out of hiding in fat, into the blood, and rapidly to the brain).

This leads to prolonged toxic effects of medications that, without additional doses, would have been rapidly cleared.